# Decision Memo for Autologous Stem Cell Transplantation (AuSCT) for Amyloidosis (CAG-00050R)

## Decision Summary

The Centers for Medicare and Medicaid Services (CMS) has determined that the evidence is adequate to conclude that when recognized clinical risk factors are employed to select patients for transplantation, high dose melphalan together with autologous stem cell transplantation (HDM/AuSCT) can provide a net health benefit for Medicare beneficiaries of any age group with primary AL amyloidosis. HDM/AuSCT is reasonable and necessary for patients of any age with primary AL amyloidosis who meet the following criteria:

- amyloid deposition in 2 or fewer organs, and
- cardiac left ventricular ejection fraction (EF) of greater than 45%.

To clarify existing coverage, autologous stem cell transplant must be used to effect hematopoietic reconstitution following severely myelotoxic doses of chemotherapy (High Dose Chemotherapy (HDCT)) and/or radiotherapy used to treat various malignancies.

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## Decision Memo

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Subject: Coverage Decision Memorandum for Reconsideration Request for Autologous Stem Cell Transplantation (AuSCT) for primary amyloid light chain (AL) Amyloidosis

Date: March 15, 2005

## I. Decision

The Centers for Medicare and Medicaid Services (CMS) has determined that the evidence is adequate to conclude that when recognized clinical risk factors are employed to select patients for transplantation, high dose melphalan together with autologous stem cell transplantation (HDM/AuSCT) can provide a net health benefit for Medicare beneficiaries of any age group with primary AL amyloidosis. HDM/AuSCT is reasonable and necessary for patients of any age with primary AL amyloidosis who meet the following criteria:

- amyloid deposition in 2 or fewer organs, and
- cardiac left ventricular ejection fraction (EF) of greater than 45%.

To clarify existing coverage, autologous stem cell transplant must be used to effect hematopoietic reconstitution following severely myelotoxic doses of chemotherapy (High Dose Chemotherapy (HDCT)) and/or radiotherapy used to treat various malignancies.

## II. Background

On June 15, 2004, CMS began a reconsideration of the national coverage determination (NCD) on high dose melphalan and autologous stem cell transplantation (HDM/AuSCT) for primary amyloid light chain (AL) amyloidosis.

AL amyloidosis is a blood disorder, associated with an abnormal condition of blood cells, in which extra-cellular insoluble protein (amyloid) fibrils accumulate in various tissues and organs throughout the body. These amyloid fibrils are formed by an errant group of plasma cells in the bone marrow and consist of abnormal immunoglobulin (Ig) light chain proteins. Except for those within the central nervous system, amyloid fibrils can affect any major organ in the body.

AL amyloidosis is a rare disease; only 1200 to 3200 new cases are reported each year in the United States.[1] Two thirds of patients with primary AL amyloidosis are male and less than 5% of patients are under 40 years of age. Both the causes and origins of primary AL amyloidosis along with the mechanism of amyloid deposition remain poorly understood.

The organs most often affected in primary AL amyloidosis include the heart, kidneys, peripheral nervous system, and gastrointestinal tract. Amyloid deposits in these organs can cause shortness of breath, fatigue, edema (swelling of ankles and legs), dizziness upon standing, a feeling of fullness in the stomach (especially after eating), diarrhea, weight loss, enlarged tongue, numbness of the legs and arms, and protein in the urine.

The clinical course of primary AL amyloidosis is usually associated with rapid disease progression, involvement of multiple organ systems, and short survival periods. Extensive organ system impairment, secondary to amyloid deposits, often results in death. Due to the rapid progression of primary AL amyloidosis, median survival from diagnosis is between one to two years, depending on which organ systems are affected. Patients with cardiac amyloid involvement have an even poorer prognosis with a median survival of less than six months, thus accounting for almost one half of deaths from primary AL amyloidosis.[1]

Because of its similarity to multiple myeloma, another plasma cell dyscrasia where plasma cells produce abnormal protein deposits, the treatment of primary AL amyloidosis has followed the same general path. The early treatment of primary AL amyloidosis largely focused around oral chemotherapy regimens. Patients were treated with standard doses of drugs such as melphalan, prednisone, and/or colchicine. Research suggested that multiple drug regimens can produce better response rates then single drug regimens. However, response rates to standard chemotherapy are quite low. For example, many patients do not live long enough to receive enough cycles of melphalan to actually benefit from treatment.

The poor response rates experienced with only chemotherapy prompted the use of HDM/AuSCT. HDM/AuSCT consists of a number of stages. The first stage is called mobilization where the patient is given a granulocyte colony-stimulating factor (G-CSF) or a granulocyte-macrophage colony-stimulating factor (GM-CSF) to stimulate the release of the stem cells from storage sites within the body prior to harvesting via leukapheresis (or bone marrow biopsy). The next stage is called conditioning where the patient is given a high dose of a chemotherapy agent, typically melphalan. In the final stage the harvested stem cells are administered along with supportive medical care.[2]

Early on, patients with AL amyloidosis who underwent HDM/AuSCT experienced a reduction in amyloid-related outcomes; however, the transplantation-related mortality was higher compared to patients with multiple myeloma. The presence and severity of amyloid-associated organ dysfunction, which can be extensive in patients with AL amyloidosis and minimal to nonexistent in patients with multiple myeloma, were determined to be the reason for the mortality discrepancy. Subsequent use of HDM/AuSCT in medical practice and studies in research trials permitted the identification of risk factors that guide the selection of patients who are most appropriate to receive HDM/AuSCT. The main factors found to be associated with a significant increased risk of morbidity or mortality includes the baseline cardiac and renal status of the patient and the extent of amyloid organ involvement (Comenzo, 2002). Cardiac ejection fraction (EF) was the clinical parameter most commonly used as an inclusion criterion in the clinical trials reviewed for this decision memorandum while the ventricular septal thickness was used less frequently. The serum creatinine level was most commonly used as an inclusion criterion in trials to identify the renal status.

**III. History of Medicare Coverage**

CMS has determined that autologous stem cell transplantation falls within the benefit category of inpatient hospital services under Part A and physicians' services under Part B. See §1812 (a)(1); §1832; §1861(s)(2); §1861(b).

On January 14, 2000, HCFA (now CMS) issued the first decision memorandum (CAG-00050N) which determined that a sufficient body of evidence does not exist to justify a national coverage decision in favor of AuSCT for patients with primary AL amyloidosis. CMS stated that we would reconsider if additional evidence was submitted in the future.

Section 110.8.1 of the National Coverage Determination (NCD) Manual states, in pertinent part, that stem cell transplantation is a process in which stem cells are harvested from either a patient's or donor's bone marrow or peripheral blood for intravenous infusion. The transplant can be used to effect hematopoietic reconstitution following severely myelotoxic doses of chemotherapy and/or radiotherapy used to treat various malignancies.

Autologous stem cell transplantation is considered reasonable and necessary under §1862(a)(1)(A) of the Act for the following conditions and is covered under Medicare for patients with:

- Acute leukemia in remission who have a high probability of relapse and who have no human leucocyte antigens (HLA)-matched;
- Resistant non-Hodgkin's or those presenting with poor prognostic features following an initial response;

- Recurrent or refractory neuroblastoma; or

- Advanced Hodgkin's disease who have failed conventional therapy and have no HLA-matched donor.

Effective October 1, 2000, single AuSCT is only covered for Durie-Salmon Stage II or III patients that fit the following requirement:

- Newly diagnosed or responsive multiple myeloma. This includes those patients with previously untreated disease, those with at least a partial response to prior chemotherapy (defined as a 50 percent decrease either in measurable paraprotein [serum and/or urine] or in bone marrow infiltration, sustained for at least 1 month), and those in responsive relapse; and

- Adequate cardiac, renal, pulmonary, and hepatic function.

NOTE: Tandem transplantation for multiple myeloma remains noncovered.

Insufficient data exist to establish definite conclusions regarding the efficacy of autologous stem cell transplantation for the following conditions:

- Acute leukemia not in remission;

- Chronic granulocytic leukemia;

- Solid tumors (other than neuroblastoma);
- Up to October 1, 2000, multiple myeloma;
- Tandem transplantation (multiple rounds of autologous stem cell transplantation) for patients with multiple myeloma;
- Effective October 1, 2000, non-primary (AL) amyloidosis; and
- Effective October 1, 2000, primary (AL) amyloidosis for Medicare beneficiaries age 64 or older.

In these cases, autologous stem cell transplantation is not considered reasonable and necessary within the meaning of §1862(a)(1)(A) of the Act and is not covered under Medicare.

**IV. Timeline of Recent Activities**

On June 15, 2004 CMS accepted Legacy Good Samaritan Hospital & Medical Center's formal request and initiated review.

On July 26, 2004, Initial public comments were posted to the tracking sheet available electronically at: http://www.cms.hhs.gov/coverage/download/id126a.pdf [PDF, 15KB].

**On December 15, 2004, CMS posted a Proposed Decision Memorandum for a 30-day public comment period pursuant to Section 731 of the Medicare Modernization Act.**

## V. FDA Status

Autologous stem cell transplantation is regulated under 21 C.F.R. §1271.3. Section 1271.3(a) defines the term autologous use as “the implantation, transportation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered.”

Section 1271.3(d)(2) defines human cells, tissues, or cellular or tissue-based products (HCT/P’s) as “ articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion or transfer into a human recipient. Examples of HCT/P’s include, but are not limited to, bone, ligament, skin, dura matter, heart valve, cornea, hematopoietic stem cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue.”

## VI. General Methodological Principles

When making national coverage decisions, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that a service or item is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) specific clinical questions relevant to the coverage request can be answered conclusively; and 2) the extent to which we are confident that the intervention will improve net health outcomes for patients. Evidence may consist of external technology assessments, internal review of published and unpublished studies, recommendations from the Medicare Coverage Advisory Committee, evidence-based guidelines, professional society position statements, expert opinion, and public comments. A fully detailed account of “General Methodological Principles of Study Design” that CMS staff utilizes to assess the relevant literature on the therapeutic or diagnostic item or service for specific conditions follows the conclusion and references for this decision memorandum (see Appendix A).

## VII. Evidence

### A. Introduction

In order to appraise the net health outcomes of HDM/AuSCT for patients with primary AL amyloidosis in comparison with standard medical therapy consisting of melphalan and prednisone and to identify any relevant patient and facility selection criteria, CMS sought to address the following question:

Is there adequate evidence to conclude that HDM/AuSCT for patients with primary AL amyloidosis improves net health outcomes for patients greater than 63 years old?

Survival, both short-term and long-term, is the primary outcome of interest. In the articles reviewed, short term survival was also referred to as treatment-related mortality, which was defined by the various study investigators as death within 90 to 100 days of HDM/AuSCT.

Hematologic response was also an outcome of interest. In clinical studies, a complete hematologic response was typically defined as a total absence of abnormal plasma cells on bone marrow examination or a lack of detection of a monoclonal gammopathy in the blood and urine.

The goal of one of the clinical studies reviewed for this decision memorandum (Seldin, 2004) was to measure changes in quality of life (QoL). This outcome was assessed using a validated instrument called the Medical Outcomes Study 36-item Short Form General Health Survey (SF-36). The SF-36 includes 36 questions to assess 8 scales of health status that are combined into 2 types of composite scores: a physical component and a mental component. The composite scores are standardized; a score of 50 corresponds to the average for the US population (standard deviation of 10). A score change of 2 to 3 units is considered to be significant.

In Seldin, 2004, the authors noted that QoL instruments exist that are specific for patients undergoing stem cell transplantation. Since patients with primary AL amyloidosis can have a wide range of symptoms due to multi-organ involvement, the SF-36 was selected because it is validated for use in a variety of diseases and patient populations.

**B. Discussion of evidence reviewed**

The evidence reviewed includes summaries of CMS's 2000 AuSCT decision memorandum, CMS's internal technology assessment of new or reconsidered evidence, as well as professional society position statements and expert opinion.

**1. Prior CMS Decision Memorandums for AuSCT**

In the 2000 decision memorandum “Autologous Stem Cell Transplantation for AL Amyloidosis” (CAG-00050N), CMS described the etiology of AL amyloidosis and treatments available, analyzed relevant clinical literature and delineated reasons for limiting Medicare's current policy of contractor discretion. [3]

In this decision memorandum CMS concluded that a sufficient body of evidence did not exist to justify a NCD in favor of AuSCT for patients with primary AL amyloidosis. The research status appeared to be preliminary and in need of long-term follow-up studies. The majority of AuSCT was performed in highly specialized, typically academic, centers thereby calling in to question the generalizability of the evidence. The clinical studies exhibited a number of deficiencies that increased the risk of bias and confounding, such as small sample sizes and a lack of a randomized control. None of the studies reviewed compared AuSCT to either a control group or other treatment modalities. Selective enrollment of patients resulted in a lack of evidence in patients over 63 years of age and in patients with non-primary AL forms of amyloidosis. Furthermore, the coverage policy in effect at the time for patients younger than 64 years was not revised due to insufficient evidence.

Safety was another concern. A wide range in treatment-related mortality (0, 12%, and 43%) was seen. This emphasized the need for controlled trials and identified proper patient selection as a critical issue to be addressed.

For Medicare beneficiaries with primary AL amyloidosis, CMS decided to not cover AuSCT for those age 64 years or older, and permitted coverage at the discretion of Medicare local contractors for those 63 years old or younger. In addition, CMS decided to not cover AuSCT for Medicare beneficiaries with nonprimary (AL) amyloidosis.

**2. External technology assessments**

Not applicable.

**3. Internal technology assessment**

**Literature Search**
CMS performed a search of the literature using the following search terms: peripheral blood, primary amyloidosis, autologous, stem cell transplant. The limitations used were: human, English, Publication date from 1/1/1999 to 11/30/2004. The databases searched were Pub Med, FirstSearch, ProQuest, and EBSCOHost.

**Summary of Evidence**
The requestor submitted 7 published articles and 4 abstracts. The published article for 1 of the abstracts was found and obtained. In addition, the requestor performed and submitted an analysis of the outcome of HDM/AuSCT for patients 65 years of age or older. Sixteen unique abstracts not previously submitted by the requestor were identified based on the following criteria: an abstract was available and the abstract presented the results of a clinical study. Of the 16 abstracts, 5 were selected for further review and the full, published article was obtained. Articles subsequently reviewed have either been newly published since CMS's 2000 decision memorandum or are previously published relevant articles now being reconsidered or referenced for the first time.

**Scientific articles**

In Skinner, 2004, the authors report the pooled results for patients enrolled in 6 distinct protocols. An unblinded, non-randomized, prospective cohort design was utilized in each study protocol. The inclusion/exclusion criteria and the treatment regimen varied across the protocols. In general, the inclusion criteria permitted patients up to 80 years of age although certain protocols were more age-restricted. Additional inclusion criteria included greater than or equal to 1 major organ involvement, an EF greater than or equal to 40%, and the presence of compensated congestive heart failure (CHF). Numerous outcomes were measured including survival and complete hematologic response.

The results from a total of 701 patients were reported. Of these 701 patients, 394 (56%) were deemed eligible and 307 were deemed ineligible for transplantation. The ineligible cohort was found to be statistically significantly different from the eligible cohort in numerous clinical features. The ineligible cohort was used as a comparison group. Only 312 of 394 eligible patients were mobilized (63 declined treatment and 19 became ineligible due to disease progression). Due to death or complications, only 277 of 312 patients were eventually transplanted.

Mean age was 56.9 years in the transplant-eligible patients and 64.6 years in the transplant-ineligible patients. Women comprised 41% and 40% of the transplant-eligible and transplant-ineligible patients, respectively.

Thirty-six of 277 patients (13%) died within 100 days of transplantation. One-year hematologic response (in 181 evaluable patients to date of which 60 were 65 years or older) was 40%. Eight percent of these patients relapsed by 2 years. No difference in rate of responders was seen in the subset of patients 65 years or older compared to younger patients.

Sanchorawala, 2003 conducted a prospective, randomized, 2-arm trial that compared the immediate administration of HDM/AuSCT (Arm 1) to an initial administration of oral melphalan and prednisone followed by high-dose melphalan and AuSCT (Arm 2). The objective was to determine whether an initial course of chemotherapy prior to HDM/AuSCT would be advantageous with respect to hematologic response and survival in newly diagnosed patients. Patients had to have an EF greater than 40% and 1 or more organs involved, but there was no upper age limit or a limit on severity of renal status if the other inclusion criteria were met. The outcome measures were survival, hematologic response, and clinical response per involved organ.

A total of 100 newly diagnosed patients were studied (52 in Arm 1; 48 in Arm 2). Patient characteristics were similar between the 2 arms except for median time from enrollment to HDM/AuSCT. The median age was 57 years in Arm 1 and 55 years in Arm 2; a range of age was not provided. Eighteen women were in each arm.

Nine patients did not complete treatment in Arm 1 due to voluntary withdrawal (4), death (2), or too ill to proceed (3). Sixteen patients did not complete treatment in Arm 2 due to voluntary withdrawal (1), withdrawal for unrelated disease (2), death (6), disease progression (3), or too ill to proceed (4).

The survival and hematologic response outcomes are presented in the following table.

| Outcomes | Arm 1 | Arm 2 |
|---|---|---|
| Treatment-related mortality # (%) | | |
| Pre-stem cell collection | 0 (0%) | 6 (13%) |
| Stem cell mobilization/collection | 5 (10%) | 7 (15%) |
| Death within 90 days of AuSCT | 5 (10%) | 4 (8%) |
| Overall Survival | | |
| 1 year | 67% | 56% |
| 2 year | 60% | 54% |
| 4 year | 51% | 50% |
| 5 year | 51% | 39% |
| Median Survival (months) | Not reported | 37 |
| Complete hematologic response at 1 year | 32% | 30% |

None of the differences were statistically significant.

Seldin, 2004 conducted a prospective, nonrandomized, unblinded, QoL assessment of patients who received HDM/AuSCT. The comparator group consisted of age-matched, transplant-ineligible patients. The purpose of the assessment was to determine if hematologic and clinical responses after HDM/AuSCT are accompanied by an increase in QoL. The outcome was measured using the physical and mental components of the SF-36 form. The hematologic and clinical response outcomes were reported in Skinner, 2004.

Two hundred and fifty-one transplanted patients were compared to 210 age-matched transplant-ineligible patients. The mean age of the transplanted patients was 56±9.5; the mean age for the comparator group was not provided. Patients were mobilized with G-CSF and conditioned with melphalan.

One hundred and four of 251 transplanted patients completed the SF-36 at baseline and at 1 year. There was no apparent difference in clinical characteristics between this group and the 147 patients who did not complete a baseline SF-36. Eighty-four transplanted patients completed the SF-36 at baseline and at 2 years. The presence or absence of differences in clinical characteristics between the 2 groups was not provided. The number of transplant-ineligible patients who completed the SF-36 at baseline and at 1 or 2 years was not provided.

The following table presents the QoL results in the transplanted patients.

| Time | Physical component score | Mental Component Score |
|---|---|---|
| Baseline | 34.5 | 45 |
| 1 year after AuSCT | 41 | 52 |
| 2 years after AuSCT | 43 | 51 |

The physical and mental component scores were not provided for the comparator group. The authors state that quality of life was found to be significantly higher for patients who had a complete hematologic response at 1 year.

A published, peer-reviewed article was not found for 3 of the 4 abstracts submitted by the requestor (Blum, 2001; Lachmann, 2002; Versole, 2003). The evidence table contains a review of these abstracts.

The fourth abstract has been published as a full, peer-reviewed article (Dispenzieri, 2004). In this article the authors report the results of a retrospective case-match-control study of 126 patients (63 cases and 63 controls; 1 case plus 1 control equals a set). Patients who underwent transplantation were matched 1:1 to patients who did not receive transplantation. Matching was based on age, sex, time to presentation, EF, serum creatinine, cardiac septal thickness, nerve involvement, 24-hour urine protein, and serum alkaline phosphatase. The outcomes measured were mortality within 100 days of transplantation and overall survival rate at 1-year, 2-years, and 4-years.

The groups were well matched for age and sex. The median age was 53 years for each group. Four sets of patients were 65 years old or older (range: 66-69 years). The only variables that demonstrated a statistically significant difference between groups at baseline were time from diagnosis to transplantation/treatment (4.4 v. 1.4 months for case v. control, respectively), and EF less than or equal to 50% (6% v. 19% for case v. control, respectively).

Mortality within 100 days of transplantation was 13%. The overall survival rates from the date of transplantation in the case and control groups are presented in the table below.

| | Case (n=63) | Control (n=63) |
|---|---|---|
| **# deaths** | 16 | 44 |
| **Overall survival rate from transplant date (%)** | | |
| **1 yr** | 82* | 68 |
| **2 yr** | 81* | 53 |
| **4 yr** | 70* | 40 |

*P<0.001

Of the 4 case patients greater than or equal to 65 years of age, 1 died at 6.3 months while the remaining 3 case patients are alive after 35, 36, and 38 months. All 4 matched control patients are deceased (death at 6.6, 6.8, 11.6, and 42.6 months).

In Dispenzieri, 2003, a retrospective analysis of the prognostic value of serum cardiac troponin levels is presented. Since this is not a clinical study that focused on the outcome of patients with primary amyloidosis who received HDM/AuSCT, this article was not reviewed.

A retrospective case report review was presented in Kumar, 2001. Since this article presents a review of gastrointestinal (GI) bleeding in 4 patients who received HDM/AuSCT, and not a clinical study that focused on determining the clinical outcomes of HDM/AuSCT, it will not be reviewed here. Similarly, Hayes-Lattin, 2002 is a presentation of 4 case reports focused on the morbidity, especially GI morbidity, associated with HDM/AuSCT.

More details for the 3 articles mentioned above can be found in the evidence table.

CMS asked the requestor to analyze any outcomes data available for patients 65 years old or older who received HDM/AuSCT. The requestor submitted the results of an analysis of data (personal correspondence, Hansen KS and Hansen LK, July 7, 2004) from articles obtained in a Medline search, the Autologous Blood and Marrow Transplant Registry (ABMTR), abstracts from the Tandem Transplant meetings (2002-2004), American Society of Hematology meetings (2001-2003), and the European Bone Marrow Transplant meetings (2001-2003), and from articles posted on the Amyloidosis Support Network website (www.amyloidosis.org).

The ABMTR database contained results for 16 patients who received HDM/AuSCT between 1997 and 2001. The 13 transplant sites were located in North and South America.

The 16 patients ranged in age from 65 to 70 years. Half of them were 65 years old. Men comprised 81% of the group. Fourteen of the 16 patients received melphalan as a single agent; 1 patient received only total body irradiation. Information for the remaining patient was not provided. The majority of patients (15/16; 94%) received a bone marrow graft while only 1 patient received a bone marrow and peripheral blood graft.

Five of the 16 patients (31%) have died. The probability (95% confidence interval) of survival at 1 year and 2 years is 75% (11%) and 63% (15%), respectively. Information regarding effectiveness was not provided.

The requestor obtained data from the Boston University School of Medicine for 61 patients who received HDM/AuSCT between 1995 and 2003. These patients were not included in the ABMTR data presented above; however, they do represent a subset of the 701 patients presented in the Skinner, 2004 article. The patient age range was 65 to 80 years. Eighty-one percent of the patients were 65 to 70 years old; 1 patient was 80 years old. Thirty-one percent were women. Information regarding the specific treatment regimens used was not provided.

Seventy-five percent of the patients were followed for at least 1 year. Median follow-up time was 19 months (range 0.5-82) for deceased patients and 51 months (range 12-100) for living patients. Treatment-related (i.e., within 100 days of transplantation) mortality was 10%. Median survival was 40 months (range 0.5-100). Thirty-nine percent of patients had a complete response at 1 year.

The European Bone Marrow Transplant Registry declined to provide data for the requestor's analysis.

The following articles were identified during the CMS literature search.

Gertz, 2000 conducted an uncontrolled, prospective cohort study of 20 patients with primary AL amyloidosis who received HDM/AuSCT. Inclusion criteria included a serum creatinine less than 2.5 mg/dL and the involvement of at least 1 organ; cardiac criteria were not stated. Patients were mobilized with cyclophosphamide and GM-CSF or G-CSF alone, and then conditioned with melphalan plus total body irradiation or melphalan alone. Hematological outcome and a variety of organ-based outcomes were measured.

Thirteen of 20 patients were alive after 3-30 months (median of 16 months) of follow-up. Twelve of 20 patients were responders with a median time to response of 4 months.

Of the 3 patients older than 64 years, 1 patient (70 year old male) died from pneumonia 2 months after transplantation, 1 patient (65 year old male) died from progressive autonomic failure and aspiration 2 months after transplantation, and 1 patient (65 year old male) is living 4 months after transplantation with a complete hematological response.

Dember, 2001 conducted a prospective, uncontrolled cohort trial in 65 patients with renal amyloidosis who were dialysis-independent and at least 18 years old. The objective was to determine the impact of HDM/AuSCT on renal amyloidosis. Inclusion criteria included an EF greater than 40% but the maximal permissible serum creatinine level or the number of involved organs was not stated. Patients were mobilized with G-CSF and conditioned with melphalan, which was dose-adjusted for age, cardiac, renal, pulmonary, and performance status. The outcome measures included 24-hour urinary protein excretion and complete hematologic response.

Median age was 57 years (range 29-77). Women comprised 43% of the patients. Six of 65 patients (9%) died during the peritransplantation period (defined as 100 days after melphalan or during stem cell mobilization or collection). Five of these 6 patients had symptomatic cardiac disease. Fifty of 65 (77%) were alive at 1 year. A comparison of the 1 year survivors versus the non-survivors showed that the survivors were younger (survivor at 1-year median age 56, range 29-71 v. non-survivor at 1-year median age 66, range 40-77, respectively [p=0.024]), had fewer number of involved organ systems, and received a higher melphalan dose. Twenty-one of the 50 1-year survivors had a complete hematologic response. Outcomes for the patients older than 63 years were not separately reported.

The Dispenzieri, 2001 article presents the results of a retrospective case series designed to determine the usefulness of transplant eligibility and other clinical parameters as a prognostic factor. Patients had to have symptomatic organ involvement, be transplant-eligible but not transplanted, and 70 years old or younger. The cardiac septal thickness had to be 15 mm or less, the EF greater than 55%, and the serum creatinine less than or equal to 2.0 mg/dL. Various chemotherapy regimens were administered. Survival was the outcome measure.

A secondary analysis of survival was also performed, which involved a 2:1 case-match-control where the control group was comprised of patients who were transplanted. The match was based on age, sex, and number of involved organs.

Follow-up was available for 96% of the patients. The median time of follow-up was 52 months (range 0.2-186 months). Median survival was 42 months (95% confidence interval, 43-57 months). Survival rates and 95% confidence intervals are presented below.

| Time | Case Survival rate% | Control Survival rate% |
|---|---|---|
| 6 months | 83 (75-92) | 85 (74-97) |
| 1-year | 74 (65-85) | 77 (65-91) |
| 2-year | 61 (54-68) | 68 (53-87) |
| 5-year | 36 (30-43) | |
| 10-year | 15 (9-24) | |

None of these differences were statistically significant.

A number of clinical parameters were found to be predictive of a poor prognosis during both univariate and multivariate analyses: an increasing number of organs involved, worsening performance status, greater than or equal to10 lb weight loss, and elevation of the serum alkaline phosphatase. Involvement of more than 2 organ systems was associated with worse survival during univariate analysis. Of note, a statistically significant survival difference was not found across the age groups (less than or equal to 50 years, 51-60 years, and 61-70 years).

Gertz, 2002 conducted a prospective, uncontrolled, case series for patients who received HDM/AuSCT between March, 1996 and January, 2001. The use of cardiac or renal status or extent of organ involvement as inclusion criteria was not stated. Sixty-six patients were mobilized with cyclophosphamide and GM-CSF, or with G-CSF alone, and then conditioned with melphalan and total body irradiation, or with melphalan alone. The outcomes measured included complete hematologic response, and various organ-based responses.

The median age was 54 years (range 31-70), and 44% were women. Overall treatment-related mortality was 14%. Thirty -three of 66 (50%) patients had a hematologic response while 32 of 66 (48%) had an organ response. In both univariate and multivariate analyses, serum creatinine and the number of involved organs were associated with mortality.

In Casserly, 2003 the results of a prospective non-randomized, unblinded, concurrent control case series are presented. Patients with amyloidosis-associated end stage renal disease (i.e., dialysis-dependent) who were treated with HDM/AuSCT were included. Patients were excluded for an EF less than 40%, oxygen saturation less than 95% on room air, a performance status greater than or equal to 3, or the presence of refractory CHF or arrhythmia. The extent of organ involvement was not stated as an inclusion/exclusion criterion.

A control group was created that consisted of patients without end stage renal disease who were treated with HDM/AuSCT during the same period. Patients were mobilized with G-CSF alone or with GM-CSF, and conditioned with melphalan. The dose of melphalan was adjusted for age, cardiac, and performance status. The outcome measures were complete hematologic response and survival.

There were 15 cases and 180 control patients. The median age for the cases was 51 years with a range of 40-67; 2 patients were older than 63 years. Females comprised 47% of the population. The demographic profile for the control patients was not provided.

Peritransplant mortality for the 15 cases (defined as death within 90 days of the start of mobilization) was 13%. The overall hematologic response rate at 1 year was 53% while the hematologic response at 1 year for only the evaluable patients was 73%. Overall median survival was 25 month, and was not statistically significantly different from that in the control group (the survival rate for the control group was not provided).

For the 2 patients who were greater than 63 years, the 67 year old woman had a complete hematologic response and died after 58 months post-transplant due to a hemorrhagic stroke, and the 64 year old woman had a complete hematologic response and is alive after 37 months.

**4. MCAC**

Not applicable.

**5. Evidence-based guidelines**

A search of the Web using Google and the search terms “evidence-based guideline” and “stem cell transplantation” yielded no documents. A search of the National Guideline Clearinghouse website was also unsuccessful.

One evidence-based guideline by the National Comprehensive Cancer Network (NCCN) was found via a link from the American Society of Clinical Oncology (ASCO) website (www.asco.org). The 2004 NCCN practice guideline for multiple myeloma briefly notes that insufficient data exist regarding the use of AuSCT for patients with primary AL amyloidosis and “therefore, all patients should be treated in the context of a clinical trial when possible.”

A 2004 guideline on the diagnosis and management of amyloidosis by the British Committee for Standards in Hematology notes that HDM/AuSCT may be considered for patients age 70 and under provided the patient has no more than 2 involved organs, does not have a history of amyloidosis-related GI bleeding, and does not have severe cardiomyopathy, advanced renal failure, or is currently on dialysis.

**6. Professional Society Position Statements**

None found.

**7. Expert Opinion**

The Comenzo, 2002 article submitted by the requestors is a review of HDM/AuSCT in patients with primary AL amyloidosis. CMS considers this article to be a source of expert opinion.

The authors extensively presented the current status of clinical practice and research, reviewed the AuSCT procedure including peri-transplantation management, and recommended a risk-adapted approach for treating patients. Points highlighted in the article include:

- Median survival of patients seen within 1 month of diagnosis was 13.2 months; less than 5% of all patients with primary AL amyloidosis survive at least 10 years from the time of diagnosis.
- Median survival for patients with CHF was 4 months.
- Patients who undergo HDM/AuSCT typically have a hematologic cancer but no organ dysfunction; patients with primary AL amyloidosis who undergo HDM/AuSCT, on the other hand, typically have multi-organ dysfunction and no cancer.
- Despite previous attempts to define risk-based criteria for patient selection, transplantation-related mortality was still 4-8 times higher in patients with primary AL amyloidosis than in patients with multiple myeloma.
- In addition to the expected risk of chemotherapy-related adverse events during HDM/AuSCT, patients with primary AL amyloidosis also have experienced enhanced toxicity, sometimes fatal, during the mobilization stage of HDM/AuSCT. The cause is unknown. The authors postulate that lower doses of G-CSF or GM-CSF may minimize the risk of toxicity.
- The extent of organ involvement prior to HDM/AuSCT directly influenced the degree of treatment-related mortality.
    - Baseline serum creatinine was a predictor for adverse chemotherapy-related survival and for the transplantation-associated development of renal failure.
    - Based on direct experience, the authors noted a peri-transplantation mortality rate of almost 100% in patients with cardiac amyloid and CHF or with a history of arrhythmia, syncope or recurrent pleural effusion.

- The authors recommended the following risk-adapted approach to selecting and treating patients with primary AL amyloidosis with HDM/AuSCT:

| | **Good risk** (any age; all criteria met) | **Intermediate risk** (age <71; either criteria) | **Poor risk** (either criteria) |
|---|---|---|---|
| **Extent of organ involvement** | 1 or 2 | 1 or 2 (must include cardiac or renal with creatinine clearance <51 mL/min) | ≥3 |
| **Cardiac involvement** | None | Asymptomatic or compensated | advanced |
| **Creatinine clearance** | ≥51 mL/min | | |

- In a further attempt to adapt treatment to the degree of risk, the authors used the above risk groups as well as the patient's age to guide the dose of melphalan to be administered during the conditioning stage of HDM/AuSCT, as presented in the table below.

**Melphalan dose adjustment**

| Good risk | Intermediate risk | Poor risk |
|---|---|---|
| 200 mg/m2 if age ≤ 60 | 140 mg/m2 if age ≤ 60 | Standard therapy |
| 140 mg/m2 if age 61-70 | 100 mg/m2 if age 61-70 | Clinical trials |
| 100 mg/m2 if age ≥ 71 | | |

A subsequent review article by Gertz, et al, published in 2004, was identified during the final 30-day comment period. In Gertz, 2004, the authors of Comenzo, 2002 provided an updated risk-adapted approach to selecting patients with primary AL amyloidosis for HDM/AuSCT and for risk-based adjustment of the melphalan dose, as presented in the tables below.

| | **Good risk (any age)** | **Intermediate risk (age <61)** | **Poor risk (either criteria)** |
|---|---|---|---|
| **Extent of organ involvement** | 1 or 2 | 1 or 2 | ≥3 |
| **Cardiac involvement** | None | Asymptomatic or compensated | Advanced |
| **Creatinine clearance** | ≥51 mL/min | <51 mL/min | |

**Melphalan dose adjustment**

| Good risk | Intermediate risk | Poor risk |
|---|---|---|

| Good risk | Intermediate risk | Poor risk |
|---|---|---|
| 200 mg/m2 if age ≤ 60 | 140 mg/m2 if age ≤ 50 | Standard therapy |
| 140 mg/m2 if age 61-70 | 100 mg/m2 if age 51-60 | Clinical trials |
| 100 mg/m2 if age ≥ 71 | | |

Selected highlights of these tables include:

- The updated risk-adapted approach to patient eligibility and melphalan dose adjustment is the same compared to the approach presented in Comenzo, 2002 with the exception of the age limit to qualify for HDM/AuSCT in the intermediate risk group: the age limit has decreased from 71 years to 61 years of age. The drop in the age limit is reflected in the melphalan dose adjustment for the intermediate risk group as well.
- The authors continue to advocate for the use of extent of organ involvement and extent of cardiac involvement as the most important criteria for patient selection for HDM/AuSCT, and ultimately for melphalan dose adjustment.
- While the extent of renal involvement (as measured by creatinine clearance) is a stated criterion, the level of renal function is used to determine the melphalan dose, but not the patient's eligibility for HDM/AuSCT.

CMS received one comment during the 30-day public comment period on the proposed decision memorandum that will be included here as an expert opinion. Dr. David Seldin, the Assistant Director of the Stem Cell Transplant Program at Boston Medical Center in Massachusetts stated that there is no evidence-based justification for limiting patient eligibility for HDM/AuSCT based on number of organs involved with amyloidosis or renal status. In questioning the decision to include renal status as a criterion Dr. Seldin referred to the Casserly, 2003 paper, which concluded that patients with end -stage renal disease (ESRD) who received HDM/AuSCT did not have significantly different outcomes compared to patients without ESRD who received HDM/AuSCT. In further support of his position, Dr. Seldin states that Skinner, 2004 found that only cardiac status and the conditioning dose of chemotherapy (e.g., melphalan) were associated with a negative survival outcome.

Dr. Seldin acknowledged the need for limiting patient eligibility based on cardiac status and recommended that the lower limit for the cardiac ejection fraction be 45% rather than 55%.

**8. Public Comments**

A. Initial 30-Day Comment Period

CMS received one initial comment that was in strong agreement with the information provided by Legacy Good Samaritan Hospital in support of coverage for HDM/AuSCT for patients with primary AL amyloidosis.

B. Final 30-Day Comment Period

During the final 30-day comment period, CMS received eleven public comments. Nine of the eleven respondents were in support of eliminating the age restriction for HDM/AuSCT for patients with primary AL amyloidosis.

Four respondents did not support the medical criteria for HDM/AuSCT listed in place of age. The first respondent states that Medicare should not be stipulating medical guidelines; doctors specializing in HDM/AuSCT should make the decision. Two respondents (1 detailed above as expert opinion) suggest that the eligibility criteria regarding organ involvement unnecessarily eliminates people from receiving HDM/AuSCT. The fourth respondent, the Amyloidosis Support Network (ASN) believes that the criteria itemized in the decision memo are unnecessary. They strongly believe that primary AL amyloidosis treatment decisions should be made between patients and doctors and CMS should incorporate the risk-adapted approach as a guideline, not as criteria for coverage. Although they do not agree with the criteria for coverage, ASN supports the registry concept and would be willing help to make the concept a reality. CMS carefully reviewed the evidence regarding criteria for HDM/AuSCT as noted in the analysis section and will modify our proposed decision in 2 ways:

- Remove the restriction based on serum creatinine level;
- Modify the restriction on cardiac left ventricular ejection fraction to greater than 45%.

**VIII. CMS Analysis**

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be “reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.” § 1862(a) (1) (A).

The quality of the studies of HDM/AuSCT conducted in patients with primary AL amyloidosis since 2000 continues to be less than robust for the Medicare elderly population. Comparative evidence from randomized, controlled trials is not available. While the majority of the studies were prospectively conducted, the majority also were non-randomized. None of the studies were blinded. A control group, when used, was either case-matched (Dispenzieri, 2001; Dispenzieri, 2004) or inappropriate (Sanchorawala, 2003; Seldin, 2004). The requestors, and a number of article authors, state that a randomized, controlled trial will probably never be conducted due to the rarity of the disease and the lack of insurance coverage for patients of Medicare age.

There is some evidence on net health outcomes for patients older than 63 years. Many studies either ultimately did not enroll many patients older than 70 years (Casserly, 2003; Dispenzieri, 2004; Gertz, 2000; Gertz, 2002; Seldin, 2004), intentionally limited enrollment to patients 70 years old or less (Dispenzieri, 2001), or did not specifically note the number of patients older than 63 years (Dember, 2001; Sanchorawala, 2003; Skinner, 2004). The age-related analysis of outcomes performed by the requestor for patients 65 years and older, by our request, provides the most evidence. The majority of patients, however, was 65 to 70 years old; only 19% of the 61 patients were older than 70 years and only 1 was 80 years old.

While most of the studies did not separately report results for patients older than 63 years, the evidence does not suggest worse survival in these patients. The Boston University data from 61 patients who were 65 years and older showed a treatment-related mortality rate of 10%, which compares favorably to the 13% treatment-related mortality rate reported for all 701 patients in Skinner, 2004. A similar overall treatment-related mortality rate was reported in Dember, 2001 (9%), Gertz, 2002 (14%), Casserly, 2003 (13%), and Dispenzieri, 2004 (13%). Dispenzieri, 2004 noted that the survival of the 4 case-matched pairs of patients 65 years old or older was slightly better for the transplant patients than for the non-transplant patients. Compared to the wide range of treatment-related mortality noted in the 2000 decision memorandum, this mortality range across studies is narrower.

Skinner, 2004 reported a median survival of 4.9 years for the subset of patients who were 65 years old and older. This finding was not statistically significantly different from the 4.6 year median survival of the younger patients. Both results contrast with the overall median survival for patients treated with standard chemotherapy of 1-1.5 years (Gertz, 2000). Hence, HDM/AuSCT for patients 63 years of age and older appears to provide a longer survival compared to the currently available treatment.

The univariate and multivariate analyses reported by Dispenzieri, 2001 provide supportive evidence since they found no statistically significant survival difference among the age groups ($\leq$50 years, 51-60 years, and 61-70 years). The multivariate analysis reported in Gertz, 2002 had similar results. Serum creatinine and the number of involved organs, but not age, were found to be independently associated with mortality. The sole study to hint at a survival difference based on the age group was Dember, 2001. Here, a comparison of the survivors and non-survivors at 1-year showed that the survivors were statistically significantly younger.

While information on patients aged 75 years and older is based on limited data, there is some evidence that HDM/AuSCT provides a benefit to this population. Therefore, the use of this treatment in the most elderly patients should be carefully considered and not routinely recommended. However, although additional evidence of risks and benefits is desirable, we will remove the previous restriction of coverage based on age.

In contrast to age, the evidence does highlight the relationship between extent of organ system involvement and HDM/AuSCT-related mortality. Results from analyses performed in Dember, 2001, Dispenzieri, 2001, and Gertz, 2002 point to greater than 2 organ involvement with amyloidosis as strongly associated with mortality, and hence a predictor of a poor prognosis. These findings serve to support the inclusion and exclusion criteria commonly used to select patients for HDM/AuSCT. Based on the findings relating number of organs involved with amyloidosis and the patient outcome of HDM/AuSCT, we are restricting coverage to those patients with amyloid deposition in 2 or fewer organs.

The Gertz, 2002 analysis found that baseline serum creatinine is independently associated with mortality. However, Casserly, 2003, demonstrated that carefully selected patients with end-stage renal disease can achieve adequate patient outcomes after HDM/AuSCT. Two sources of expert opinion (Gertz, 2004, and Dr. David Seldin) do not call for the use of renal status as a criterion for patient eligibility. We have concluded that coverage does not need to be restricted based upon renal status, and therefore, we are deleting the serum creatinine standard that was discussed in the proposed in the proposed decision memorandum. The relationship between cardiac status and patient outcomes, especially mortality, is well established by numerous studies as noted in Comenzo, 2002. This is acknowledged by both Gertz, 2004 in the risk-based patient eligibility criteria, and by Dr. Seldin. In the articles reviewed for this decision memorandum the range of EF as an inclusion criterion was 40-55%. CMS agrees with the comment regarding the minimum acceptable cardiac EF necessary for eligibility, and has modified the restriction to limit coverage to those persons with EF of greater than 45%.

The majority of the studies reviewed for this decision memorandum were conducted in the Stem Cell Transplant Program and the Amyloid Treatment and Research Program at the Boston University School of Medicine in Boston, MA or in the Division of Hematology and Internal Medicine at the Mayo Clinic in Rochester, MN. Additional institutions included the Bone Marrow Transplantation and Leukemia Program at the Washington University School of Medicine in St. Louis, MO; the National Amyloidosis Centre at the Royal Free and University College Medical School in London, UK; the Medical College of Wisconsin in Milwaukee, WI; and the Hematology Service of the Department of Medicine at the Memorial Sloan-Kettering Cancer Center in NY, NY.

The preponderance of major academic institutions in the medical literature signifies the diversity and magnitude of resources necessary to appropriately care for patients with primary AL amyloidosis who undergo treatment with HDM/AuSCT. This point is highlighted by the creation in 1996 of the Foundation for the Accreditation of Cellular Therapy (FACT; www.factwebsite.org) to establish and maintain standards for the safe collection, processing, and administration of hematopoietic cells. It is unlikely that the evidence and results reviewed in this decision memorandum can be readily generalized to facilities with significantly less resources than that typically found at an institution with a hematopoietic transplantation program.

Finally, we desire to ensure that HDM/AuSCT is performed only in those patients who are most likely to benefit (i.e., in those patients who have a confirmed diagnosis of the AL form of amyloidosis, and not the AA or AF forms) and that the procedures are done only by competent providers in facilities with a history of good outcomes and a quality assessment/improvement program to identify providers with poor outcomes and other areas for improvement. A formal data collection system, such as a registry, is one mechanism to address the above needs and concerns. The submission of surveillance data on patients receiving HDM/AuSCT for AL amyloidosis to a DCS will help to assure patient safety and protection. Data will help identify the appropriate patients to receive HDM/AuSCT for AL amyloidosis and help reduce the incidence of inappropriate therapy.

**IX. Decision**

The Centers for Medicare and Medicaid Services (CMS) has determined that the evidence is adequate to conclude that when recognized clinical risk factors are employed to select patients for transplantation, high dose melphalan together with autologous stem cell transplantation (HDM/AuSCT) can provide a net health benefit for Medicare beneficiaries of any age group with primary AL amyloidosis. HDM/AuSCT is reasonable and necessary for patients of any age with primary AL amyloidosis who meet the following criteria:

- amyloid deposition in 2 or fewer organs, and
- cardiac left ventricular EF of greater than 45%.

To clarify existing coverage, autologous stem cell transplant must be used to effect hematopoietic reconstitution following severely myelotoxic doses of chemotherapy (High Dose Chemotherapy (HDCT)) and/or radiotherapy used to treat various malignancies.

**Appendix A: General Methodological Principles**

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the relevance of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention’s risks and benefits.

The issues presented here represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has unique methodological aspects.

**1. Assessing Individual Studies**

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias;
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups;
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes;
- Larger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found;
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias);
- Co-interventions or provision of care apart from the intervention under evaluation (confounding);
- Differential assessment of outcome (detection bias);
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials;
- Non-randomized controlled trials;
- Prospective cohort studies;
- Retrospective case control studies;
- Cross-sectional studies;
- Surveillance studies (e.g., using registries or surveys);
- Consecutive case series;

- Single case reports.

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study's selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess the evidence.

**2. Generalizability of Clinical Evidence to the Medicare Population**

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage decisions for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess net health outcomes, and we are interested in the results of changed patient management not just altered management. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

**3. Assessing the Relative Magnitude of Risks and Benefits**

An intervention is not reasonable and necessary if its risks outweigh its benefits. Among other things, CMS evaluates whether reported benefits translate into improved net health outcomes. The direction, magnitude and consistency of the risks and benefits across studies are important considerations. Based on the analysis of the strength of the evidence, CMS assesses whether an intervention or technology's benefits to Medicare beneficiaries outweigh its harms.

**Appendix B: Evidence Table** [PDF, 219KB]

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[1] http://amyloidosis.org/treatment/primary.asp#primary

[2] High dose chemotherapy and stem cell transplantation are not reasonable and necessary when given separately. CMS considers the combination to be a single course of treatment.

[3] http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=9

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